

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 47/40	A1	(11) International Publication Number: WO 00/12137 (43) International Publication Date: 9 March 2000 (09.03.00)
(21) International Application Number: PCT/US99/20060 (22) International Filing Date: 1 September 1999 (01.09.99) (30) Priority Data: 60/098,854 2 September 1998 (02.09.98) US (71) Applicant: ALLERGAN SALES, INC. [US/US]; 2525 Dupont Drive, Irvine, CA 92612 (US). (72) Inventors: BECK, Gary, J.; 2085 Smokewood Avenue, Fullerton, CA 92831 (US). KERSLAKE, Edward, D., S.; 30 Elm Street #1, Charlestown, MA 02129 (US). OLEJNIK, Orest; 18 Golden Poppy Drive, Coto De Caza, CA 92679 (US). (74) Agents: FISHER, Carlos, A. et al.; Allergan Sales, Inc., 2525 Dupont Drive, Irvine, CA 92612 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: PRESERVED CYCLODEXTRIN-CONTAINING COMPOSITIONS (57) Abstract Compositions including a liquid medium, a cyclodextrin component and a preservative component which has a reduced tendency to being complexed with the cyclodextrin component. In one embodiment, the preservative component is a chlorite component. Active components, such as pharmaceutically active components or drugs, preferably are included in the compositions.		

Best Available Copy

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PRESERVED CYCLODEXTRIN-CONTAINING COMPOSITIONS

RELATED APPLICATION

This application claims benefit of Provisional Application Serial No. 60/098,854 filed September 2, 1998.

BACKGROUND OF THE INVENTION

The present invention relates to preserved cyclodextrin-containing compositions. More particularly, the invention relates to cyclodextrin-containing compositions, for example, such compositions containing one or more pharmaceutically active components, including preservatives which have substantial preserving efficacy in the presence of cyclodextrin components.

Cyclodextrins are widely known in the literature to increase the solubility of poorly water soluble pharmaceuticals or drugs and/or enhance pharmaceutical/drug stability and/or reduce unwanted side effects of pharmaceuticals/drugs. For example, steroids, which are hydrophobic, often exhibit an increase in water solubility of one order of magnitude or more in the presence of cyclodextrins. However, one substantial problem with pharmaceutical compositions including cyclodextrins, particularly such compositions in multi-dose formats, has to do with preserving such compositions. Typical preservatives are relatively ineffective at normal concentrations in such compositions, that is the compositions including such preservatives are unable to meet or pass standard preservative efficacy tests. It is believed that the preservative becomes complexed with the cyclodextrin and is rendered ineffective or has reduced effectiveness as a preservative.

It would be advantageous to provide cyclodextrin-containing compositions which are effectively preserved.

SUMMARY OF THE INVENTION

New cyclodextrin-containing compositions have been
5 discovered. Such compositions include preservatives which
are effective and efficacious in the presence of
cyclodextrins. Preferably, the preservatives are present
in the compositions in amounts to provide acceptable
preservative efficacy and, in addition, are sufficiently
10 innocuous or non-toxic so that the compositions can be
administered to humans or animals to obtain desired
therapeutic effects without significant detriment
resulting from the presence of the preservatives. For
example, the present compositions may include a
15 pharmaceutical effective in providing a therapeutic effect
when administered to the eyes of a human or animal. The
preservative employed is preferably ophthalmically
acceptable at the concentration employed so that the human
or animal is effectively treated without significant harm
20 caused by the presence of the preservative.

In short, the present compositions effectively take
advantage of cyclodextrin components, e.g., in increasing
the apparent water solubility of pharmaceuticals, and are
effectively preserved and preferably substantially non-
25 toxic in use.

In one broad aspect of the present invention,
compositions are provided which comprise a liquid medium,
a cyclodextrin component, for example, in an amount in the
range of about 0.1% to about 30% (w/v), and a preservative
30 component in an effective preserving amount, preferably of
less than about 1% (w/v) or about 0.8% (w/v) and may be in
the range of about 10 ppm(w/v) or less to about 200
ppm(w/v). In one embodiment, the preservative component

has sufficient preservative efficacy so that the composition including such preservative component passes one or more standard preservative efficacy tests, such as in the United States Preservative Efficacy Test (USPET),
5 the European Preservative Efficacy Test-A (EP-A), the European Preservative Efficacy Test-B (EP-B), and the like standard tests.

Preferably, the preservative component has an increased or greater preservative efficacy in the present
10 composition relative to an identical amount (w/v) of benzalkonium chloride. Benzalkonium chloride, which is a preservative that is often used in pharmaceutical compositions, is relatively ineffective at typical concentrations in compositions including cyclodextrin
15 component. It is believed that the benzalkonium chloride complexes with the cyclodextrin component. This complex renders the benzalkonium chloride antimicrobially ineffective. Thus, benzalkonium chloride has a reduced preservative efficacy in the presence of cyclodextrin
20 component. More preferably, the present preservative component forms a complex with the cyclodextrin component, if at all, to a lesser extent than does benzalkonium chloride.

The present compositions preferably are substantially
25 free of inclusion complexes of the cyclodextrin component and the preservative component.

Using a preservative component in accordance with the present invention which is substantially not affected by the cyclodextrin component allows the preservative
30 component to be more efficacious as a preservative. Alternately, reduced amounts of the preservative component can be used to achieve acceptable preservative results. Such reduced amounts of preservative components reduce the

toxicity or sensitivity for the composition as it is being administered to a human or animal.

Any suitable preservative component which functions as described herein is included within the scope of the present invention. The preservative efficacy tests identified herein are standard tests which can be easily and routinely conducted on any prospective preservative component to determine if such preservative component meets the criteria. Of course, the present preservative components should have no substantial detrimental effect on the composition or the active component or components of the composition or the use of the composition or the human or animal to whom the composition is administered. Tests to determine whether a prospective preservative component meets these criteria are well known and can be routinely conducted. In other words, one of ordinary skill in the art can determine, without undue experimentation, whether or not any prospective preservative component is within the scope of the preservative components of the present invention.

In one particularly useful embodiment, the present preservative component is selected from chlorite components, sorbic acid components and mixtures thereof present in an effective preserving amount. More preferably, the preservative component is selected from stabilized chlorine dioxide, alkali metal chlorites, sorbic acid, alkali metal sorbates and mixtures thereof. Chlorite components are very effective in the present compositions since they achieve preservative effectiveness at a relatively reduced concentration. Both the chlorite components and sorbic acid components are effective preservatives in the presence of cyclodextrin. Without wishing to limit the invention to any particular theory of operation, it is believed that the chlorite components and

the sorbic acid components are substantially free in the presence of the cyclodextrin component or are substantially not complexed with the chlorodextrin component.

5 In another broad aspect of the present invention, compositions are provided which comprise a liquid medium, an active component, a cyclodextrin component and a preservative component. The active component is present in an amount effective in providing a desired effect to a
10 human or an animal after the composition is administered to the human or animal. The cyclodextrin component preferably is present in an amount effective to increase the apparent solubility of the active component in the liquid medium and/or enhance the stability of the active
15 component in the composition and/or reduce unwanted side effects of the acting component in the composition. The preservative component is present in an effective preserving amount, preferably less than about 1% (w/v) or about 0.8% (w/v) and may be in the range of about 10
20 ppm(w/v) or less to about 200 ppm(w/v). The preservative component is as identified elsewhere herein.

The present compositions which include active components, preferably pharmaceutically active components, as described herein, are particularly useful in multi-dose
25 formats in which preservative efficacy is particularly important. Thus, such compositions obtain the advantages of cyclodextrin components, for example, in enhancing the solubility of the active components and, in addition, include effective preservative components, preferably at
30 concentrations which reduce the risk of causing any substantial or significant harm or detriment to the humans or animals to whom the compositions are administered as a result of the presence of the preservative components.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent.

- 5 Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

DETAILED DESCRIPTION

- 10 The present compositions include liquid media, cyclodextrin components, and preservative components. Preferably, the present compositions further include active components, more preferably pharmaceutically active components. The present compositions can have the characteristics of simple liquid, for example, aqueous
15 liquid, solutions.

- Any suitable cyclodextrin component may be employed in accordance with the present invention. The useful cyclodextrin components include, but are not limited to, those materials which are effective in increasing the
20 apparent solubility, preferably water solubility, of poorly soluble active components and/or enhance the stability of the active components and/or reduce unwanted side effects of the active components. Examples of useful cyclodextrin components include, but are not limited to:
25 α -cyclodextrin, derivatives of α -cyclodextrin, β -cyclodextrin, derivatives of β -cyclodextrin, γ -cyclodextrin, derivatives of γ -cyclodextrin, carboxymethyl- β -cyclodextrin, carboxymethyl-ethyl- β -cyclodextrin, diethyl- β -cyclodextrin, dimethyl- β -
30 cyclodextrin, methyl- β -cyclodextrin, random methyl- β -cyclodextrin, glucosyl- β -cyclodextrin, maltosyl- β -cyclodextrin, hydroxyethyl- β -cyclodextrin, hydroxypropyl- β -cyclodextrin, sulfobutylether- β -cyclodextrin, and the

like and mixtures thereof. As used herein, the term "derivatives" as it relates to a cyclodextrin means any substituted or otherwise modified compound which has the characteristic chemical structure of a cyclodextrin sufficiently to function as a cyclodextrin component, for example, to enhance the solubility and/or stability of active components and/or reduce unwanted side effects of the active components and/or to form inclusive complexes with active components, as described herein.

10 The specific cyclodextrin component selected should have properties acceptable for the desired application. The present compositions, and therefore the cyclodextrin component, may be applied topically and/or systemically. Topical application is preferred. In certain situations, 15 the cyclodextrin component should have or exhibit reduced toxicity, particularly if the composition is to be exposed to sensitive body tissue, for example, eye tissue, etc. Very useful cyclodextrin components include β -cyclodextrin, derivatives of β -cyclodextrin and mixtures thereof. 20 Particularly useful cyclodextrin components include sulfobutylether β -cyclodextrin, hydroxypropyl β -cyclodextrin and mixtures thereof. Sulfobutylether β -cyclodextrin is especially useful, for example, because of its substantially reduced toxicity.

25 The amount of cyclodextrin component in the present compositions is not of critical importance. Such amount should be effective to perform the desired function or functions in the present composition and/or after administration to the human or animal. The amount of 30 cyclodextrin component preferably is sufficient to complex at least in major amount, and more preferably substantially all, of the active component in the present composition. In one useful embodiment, the amount of cyclodextrin component in the present composition is in

the range of about 0.1% to about 30% (w/v) or more of the composition.

5 The present preservative components are selected so as to be effective and efficacious as preservatives in the present compositions, that is in the presence of cyclodextrin components, and preferably have reduced toxicity and more preferably substantially no toxicity when the compositions are administered to a human or animal.

10 As stated above, preservatives which are commonly used in pharmaceutical compositions are often less effective when used in the presence of cyclodextrins. In certain instances, this reduced preservative efficacy can be compensated for by using increased amounts of the preservative. However, where sensitive or delicate body
15 tissue is involved, this approach may not be available since the preservative itself may cause some adverse reaction or sensitivity in the human or animal, to whom the composition is administered.

20 Preferably, the present preservative components are effective in concentrations of less than about 1% (w/v) or about 0.8% (w/v) and may be 500 ppm (w/v) or less, for example, in the range of about 10 ppm(w/v) or less to about 200 ppm(w/v). In one embodiment, the present
25 preservative components have greater preservative efficacy in the composition relative to an identical amount (w/v) of benzalkonium chloride in the presence of the cyclodextrin component. Testing to determine comparative preservative efficacy is well known and can be routinely
30 conducted. Preservative components in accordance with the present invention preferably include, but are not limited to, those which form complexes with the cyclodextrin component to a lesser extent than does benzalkonium chloride.

Very useful examples of the present preservative components include, but are not limited to, chlorite components, sorbic acid components and mixtures thereof.

Specific examples of chlorite components useful as
5 preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures therefor. Technical grade (or USP grade) sodium chlorite is a very useful
10 preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its
15 entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide by International Dioxide, Inc. An especially useful SCD is a product sold
20 under the trademark Purogene® by Bio-Cide International, Inc.

Specific examples of sorbic acid components useful as preservatives in accordance with the present invention include sorbic acid itself, as well as pharmaceutically
25 and/or ophthalmically acceptable sorbic acid derivatives and mixture thereof. Useful sorbic acid components include, but are not limited to, metal sorbates, such as alkali metal and alkaline earth metal sorbates, and the like and mixtures thereof. If a sorbic acid component is
30 employed as a preservative in accordance with the present invention, the composition advantageously has a pH of less than about 7, for example in the range of about 3 or about 4 to less than 7. Such pH conditions increase the antimicrobial effectiveness of the sorbic acid component

so that somewhat reduced concentrations of the sorbic acid component may be effectively employed. Of course, it is not essential that the composition have a pH of less than 7.

5 The preservative component may be included in the composition at a predetermined concentration, e.g., to provide an effective preserving amount of preservative component in the composition. For example, if a chlorite
10 the present invention, the concentration of the chlorite component preferably is less than about 500 ppm (w/v), and more preferably is in the range of about 10 ppm (w/v) or less to about 200 ppm (w/v). If a sorbic acid component
15 is employed as a preservative, the concentration of the sorbic acid component preferably is in the range of less than about 1% (w/v) or about 0.8% (w/v), and more preferably is in a range of about 0.05% (w/v) or less to about 0.8% (w/v).

20 The presently useful active components preferably are chosen to benefit from the presence of the cyclodextrin components. In general, the active components are provided with increased apparent solubility, preferably increased apparent water solubility, by the presence of the cyclodextrin components. Without wishing to limit the
25 invention to any particular theory of operation, it is believed that the active components form inclusion or clathrate complexes with the cyclodextrin components.

30 Examples of the pharmaceutically active component which may be benefitted by the presence of cyclodextrin components in the present invention include, but are not limited to, diphenyl hydantoin, adiphenine, allobarbitol, aminobenzoic acid, amobarbital, ampicillin, anethole, aspirin, azopropazone, azulene barbituric acid, beclomethasone, beclomethasone dipropionate, bencyclane,

benzaldehyde, benzocaine, benzodiazepines,
benzodiazepines, benzothiazide, betamethasone,
betamethasone 17-valerate, bromobenzoic acid
bromoisovalerylurea, butyl-p-aminobenzoate,
5 chloralhydrate, chlorambucil, chloramphenicol,
chlorobenzoic acid, chlorpromazine, cinnamic acid,
clofibrate, coenzyme A, cortisone, cortisone acetate,
cyclobarbitol, cyclohexyl anthranilate, deoxycholic acid,
dexamethasone, dexamethasone acetate, diazepam, digitoxin,
10 digoxin, estradiol, flufenamic acid, fluocinolone
acetone, 5-fluorouracil, flurbiprofen, griseofulvin,
guaiaculene, hydrocortisone, hydrocortisone acetate,
ibuprofen, indican, indomethacin, iodine, ketoprofen,
lankacidin-group antibiotics, mefenamic acid, menadione,
15 mephobarbital, methbarbital, methicillin, metronidazole,
mitomycin, nitrazepam, nitroglycerin, nitrosureas,
paramethasone, penicillin, pentobarbital, phenobarbital,
phenobarbitone, phenyl-butyric acid, phenyl-valeric acid,
phenytoin, prednisolone, prednisolone acetate, prednisone,
20 progesterone, propylparaben, proscillaridin, prostaglandin
A series, prostaglandin B series, prostaglandin E series,
prostaglandin F series, quinoline anti-microbials
reserpine, spironolactone, sulfacetamide sodium,
sulfonamide, androgens, including but not limited to
25 testosterone, thalidomide, thiamine dilaurylsulphate,
thiamphenicolpalmitate, thiopental, triamcinolone, vitamin
A, vitamin D3, vitamin E, vitamin K3, and warfarin.

The complexes may be prepared by any method known in
the art for the preparation of complexes of cyclodextrin
30 components. For example, the active component and
cyclodextrin component may be dissolved in water or an
organic solvent (either miscible or immiscible with
water). Convenient solvents include for example
diethylether, tetrahydrofuran, dioxane, acetone,

dimethylsulfoxide, dimethylformamide and lower aliphatic alcohols. Preferably the active component is dissolved in either water or a mixture of water and a water-miscible solvent such as methanol or ethanol. The active component
5 may also be suspended in water.

After equilibrium is reached, the complex may be isolated by any suitable technique for example, lyophilization, evaporation of the solvent, precipitation, low temperature crystallization, or spray-drying.
10 Cyclodextrin inclusion complexes may also be produced by physically grinding or kneading the cyclodextrin component and the active component with or without a small amount of solvent. The ratio of cyclodextrin component to active component used to prepare the complexes may be any
15 convenient ratio but the cyclodextrin component preferably is used in a molar excess.

Benefits may be obtained by having the molar ratio of cyclodextrin component to active component in the range of about 10:1 to about 1:1 or less, preferably about 5:1 or
20 about 3:1 or about 2:1 to about 1:1 or less and by using the methods and ratios described above. Complexes are conveniently obtained containing up to 20% w/w of the active component. However, in view of the low doses of the drug normally administered and the difficulty of
25 preparing homogenous mixtures of active ingredient and excipients it may be desirable to prepare the complex with an excess of the cyclodextrin component present, for example, complexes containing in the order of about 0.001% to about 10% by weight of the active component.

30 The liquid media useful in the present invention are selected to have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. The liquid media are preferably aqueous-

based. One useful aqueous liquid medium is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution. The aqueous liquid medium preferably has a pH in the range of about 4 or about 6 to about 9 or about 10, more preferably about 6 to about 8. In one embodiment, liquid medium preferably has a ophthalmically acceptable tonicity level, for example, of at least about 200 mOsmol/kg, more preferably in the range of about 200 to about 600 mOsmol/kg.

10 In order to insure that the pH of the aqueous liquid medium is maintained within the desired range, the aqueous liquid medium may include at least one buffer component. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components
15 are advantageously used in the present invention.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid medium and do not have deleterious or toxic properties which could harm the human
20 or animal to whom the present compositions are administered. Example of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof.
25 In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil
30 liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring agents, surface active agents, thickeners, lubricants, and the like, for example, such additional

ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof. Such aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral

oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gum tragacanth, naturally-occurring phosphatides, for example, 5 soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate. The emulsions may 10 also contain sweetening and flavoring agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring 15 agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, 20 route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

The active component in the present compositions may be administered at dosage levels and dosage intervals 25 required to achieve the desired therapeutic effect normally associated with the active component and the disease or condition state in absence of the cyclodextrin component.

The following non-limiting examples illustrate 30 certain aspects of the present invention.

EXAMPLES 1 AND 2

Two (2) aqueous compositions were prepared by blending together the following components:

	<u>Components</u>	<u>Composition 1</u>	<u>Composition 2</u>
5	Sodium chloride	0.62% (w/v)	0.62% (w/v)
	Potassium chloride	0.14% (w/v)	0.14% (w/v)
	Calcium chloride (dihydrate)	0.02% (w/v)	0.02% (w/v)
	Magnesium chloride (hexahydrate)	0.006% (w/v)	0.006% (w/v)
	Sodium carboxymethylcellulose	0.5% (w/v)	0.5% (w/v)
10	Boric acid	0.2% (w/v)	0.2% (w/v)
	Sodium borate (decahydrate)	0.14% (w/v)	0.14% (w/v)
	Brimodine tartarate ⁽¹⁾	0.2% (w/v)	0.2% (w/v)
	Stabilized chlorine dioxide ⁽²⁾	50 ppm (w/v)	50 ppm (w/v)
	Sulfobutylether β cyclodextrin	---	1% (w/v)
15	Water, USP	Q.S. to volume	Q.S. to volume
	pH	7.4	7.4

⁽¹⁾ Tartarate of 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline

⁽²⁾ Product sold by Bio-Cide International Inc., under the trademark PUROGENE[®]

20 Each of these compositions was tested for preservative efficacy in accordance with (1) United States Preservative Efficacy Test (USPET) test criteria; (2) European Preservative Efficacy-A (EP-A) test criteria; and (3) European Preservative-B (EP-B) test criteria.

25 These test criteria are well known and conventionally utilized to determine the preservative efficacy of any given preservative or preserved composition.

The test results for each of these compositions is set forth in the following table.

30	<u>Composition</u>	<u>USPET</u>	<u>EP-A</u>	<u>EP-B</u>
	1	Pass	Fail	Fail
	2	Pass	Fail	Pass

These test results show that Composition 1 passes the USPET test criteria, and fails the EP-A and EP-B test

35 criteria. The EP-B criteria were failed marginally by

Composition 1 against C. Albicans. It is believed that composition 1 may pass the EP-B test criteria upon retest.

Composition 2 passes both the USPET and the EP-B test criteria and fails only the more strict EP-A test criteria.

These results demonstrate that the presence of a cyclodextrin component (Composition 2) does not have any detrimental effect on the preservative efficacy of stabilized chlorine dioxide, a chlorite component. These results indicate that the stabilized chlorine dioxide remains free and effective as a preservative in Composition 2, rather than being complexed by the cyclodextrin component and thus inhibited in providing preservative efficacy.

Composition 2, in accordance with the present invention, is ophthalmically acceptable and effective in providing therapeutic effects resulting from the presence of the brimonidine tartarate. The presence of the cyclodextrin component in Composition 2 enhances the effective or apparent water solubility of the brimonidine tartarate, substantially without detrimentally causing increased toxicity, for example, when administered to a patient in need of the therapeutic effects provided by brimonidine tartarate.

EXAMPLES 3 TO 9 (Comparative)

A series of seven (7) aqueous compositions were prepared by blending together the following components:

<u>Composition</u>	<u>Benzalkonium Chloride</u>	<u>Hydroxybutyl β cyclodextrin</u>	<u>Water</u>	<u>pH</u>
3	50 ppm (w/v)	20% (w/v)	Q.S. to vol.	8.0
4	100 ppm (w/v)	20% (w/v)	Q.S. to vol.	8.0
5	50 ppm (w/v)	10% (w/v)	Q.S. to vol.	7.2
6	50 ppm (w/v)	10% (w/v)	Q.S. to vol.	8.0
7	50 ppm (w/v)	10% (w/v)	Q.S. to vol.	8.0
8	50 ppm (w/v)	---	Q.S. to vol.	7.2
9	50 ppm (w/v)	---	Q.S. to vol.	8.0

Each of these aqueous compositions was tested for preservative efficacy in accordance with the USPET test criteria. Results of these tests are summarized in the following table.

5	<u>Composition</u>	<u>USPET Results</u>
	3	Fail
	4	Fail
	5	Fail
	6	Fail
10	7	Fail
	8	Pass
	9	Pass

These test results indicate that benzalkonium chloride is ineffective as a preservative when used in compositions including cyclodextrin components. Without wishing to limit the invention to any particular theory of operation, it is believed that the cyclodextrin component complexes the benzalkonium chloride sufficiently to inhibit or even prevent the benzalkonium chloride from being an effective preservative.

These results are in substantial contrast to the results set forth in Examples 1 and 2 in which stabilized chlorine dioxide is shown to be an effective preservative with or without a cyclodextrin component.

25

EXAMPLES 10 TO 21

A series of twelve (12) aqueous compositions were prepared by blending together the following components:

19

Composition ⁽¹⁾

		<u>10</u>	<u>11</u>	<u>12</u>	<u>13</u>	<u>14</u>	<u>15</u>
	Prednisolone						
	Acetate, w/v%	-	-	-	-	0.1	0.1
5	Sulfobutylether						
	β -cyclodextrin, w/v%	-	-	8.0	8.0	8.0	8.0
	Benzalkonium						
	chloride, w/v%	0.15	.0075	0.15	.0075	0.15	.0075
10	Stabilized chlorine						
	dioxide ⁽²⁾ , w/v%	-	-	-	-	-	-

Composition ⁽¹⁾

		<u>16</u>	<u>17</u>	<u>18</u>	<u>19</u>	<u>20</u>	<u>21</u>
	Prednisolone						
	Acetate, w/v%	-	-	-	-	0.1	0.1
15	Sulfobutylether						
	β -cyclodextrin, w/v%	-	-	8.0	8.0	8.0	8.0
	Benzalkonium						
	chloride, w/v%	-	-	-	-	-	-
20	Stabilized chlorine						
	dioxide ⁽²⁾ , w/v%	0.15	.0075	0.15	.0075	0.15	.0075

(1) Each of the compositions includes USP water in a quantity sufficient to equal 100% w/v.

(2) Product sold by Bio-Cide International Inc., under the trademark PUROGENE®

5 Each of these compositions was tested for preservative efficacy in accordance with (1) United States Preservative Efficacy Test (USPET) test criteria; (2) European Preservative Efficacy-A (EP-A) test criteria; and (3) European Preservative-B (EP-B) test criteria.

10 The test results for each of these compositions is set forth in the following table.

	<u>Composition</u>	<u>USPET</u>	<u>EP-A</u>	<u>EP-B</u>
	10	Pass	Pass	Pass
	11	Pass	Pass	Pass
15	12	Fail	Fail	Fail
	13	Fail	Fail	Fail
	14	Fail	Fail	Fail
	15	Fail	Fail	Fail
	16	Pass	Fail	Fail
20	17	Pass	Fail	Fail
	18	Pass	Fail	Fail
	19	Pass	Fail	Fail
	20	Pass	Fail	Fail
	21	Pass	Fail	Fail

25 Compositions 10 and 11, which include only benzalkonium chloride, pass all of the preservative efficacy criteria. On the other hand, compositions 12 to 15, which include benzalkonium chloride and the cyclodextrin fail all preservative efficacy criteria. The
30 addition of prednisolone acetate does not help to increase the antimicrobial activity, except for the activity

against S. Aureus. All of the solutions, that is Compositions 16 to 21, containing stabilized chlorine dioxide pass the USPET. Compositions containing only stabilized chlorine dioxide, that is Compositions 16 and 5 17, fail the EP-A and EP-B tests on fungi only. When the cyclodextrin is added to the compositions including stabilized chlorine dioxide, Compositions 18 to 21, the antimicrobial activity is decreased. Compositions containing stabilized chlorine dioxide, the cyclodextrin, 10 and prednisolone acetate, Compositions 20 and 21, fail the EP-A and EP-B criteria for the fungi only. The compositions including stabilized chlorine dioxide only fail the EP-B test only for A. Niger.

Although the presence of the cyclodextrin component 15 does result in a decrease in the antimicrobial activity of the compositions, the combination of the cyclodextrin component and stabilized chlorine dioxide, a chlorite component, passes the preservative efficacy tests passed by compositions including only stabilized chlorine 20 dioxide. These results indicate that a substantial portion of the stabilized chlorine dioxide remains free or not complexed by the cyclodextrin and effective as a preservative rather than being complexed by the cyclodextrin component and thus inhibited in providing 25 preservative efficacy.

EXAMPLES 22 TO 29

A series of eight (8) aqueous compositions were prepared by blending together the following components:

22

Composition ⁽¹⁾

	22	23	24	25
Prednisolone				
Acetate, w/v%	0.1	0.1	0.1	0.1
5 Sulfobutylether				
β -cyclodextrin, w/v%	8.0	8.0	8.0	8.0
Benzalkonium				
chloride, w/v%	0.15	0.15	0.15	0.15
Stabilized chlorine				
10 dioxide ⁽²⁾ , w/v%	-	-	-	-
Potassium				
sorbate, w/v%	.05	.5	-	-
Glycerin, w/v%	-	-	2.0	-
Propyl glycol, w/v%	-	-	-	2.0

15

Composition ⁽¹⁾

	26	27	28	29
Prednisolone				
Acetate, w/v%	0.1	0.1	0.1	0.1
Sulfobutylether				
20 β -cyclodextrin, w/v%	8.0	8.0	8.0	8.0
Benzalkonium				
chloride, w/v%	-	-	-	-
Stabilized chlorine				
dioxide ⁽²⁾ , w/v%	.0075	.0075	.0075	.0075
25 Potassium				
sorbate, w/v%	.05	.5	-	-
Glycerin, w/v%	-	-	2.0	-
Propyl glycol, w/v%	-	-	-	2.0

(1) Each of the compositions includes USP water in a quantity sufficient to equal 100% w/v.

(2) Product sold by Bio-Cide International Inc., under the trademark PUROGENE®

5 Each of these compositions was tested for preservative efficacy in accordance with (1) United States Preservative Efficacy Test (USPET) test criteria; (2) European Preservative Efficacy-A (EP-A) test criteria; and (3) European Preservative-B (EP-B) test criteria.

10 The test results for each of these compositions is set forth in the following table.

	Composition	USPET	EP-A	EP-B
	22	Fail	Fail	Fail
	23	Fail	Fail	Fail
15	24	Fail	Fail	Fail
	25	Fail	Fail	Fail
	26	Pass	Fail	Fail
	27	Pass	Fail	Pass
	28	Pass	Fail	Fail
20	29	Pass	Fail	Fail

These results indicate that all benzylkonium chloride-containing compositions fail all of the USPET, EP-A and EP-B criteria.

25 With regard to compositions including stabilized chlorine dioxide, Compositions 26, 28 and 29 fail the EP-A and EP-B criteria because of either or both *C. albicans* and *A. niger* or just *A. niger*. Each of these compositions pass the USPET criteria. Composition 27 shows interesting results. This composition fails the EP-A criteria for *C.*
 30 *albicans* and *A. niger*, but passes both USPET and EP-B

criteria. Upon repeat of the test, the composition passes the EP-A criteria.

The potassium sorbate even has an effect on the benzalkonium chloride-containing composition, that is
 5 Composition 23. Composition 23 still fails the USPET criteria, but only because of *E. coli* and *A. niger*. Other samples fail because of *P. aerogenosa*. Thus, the potassium sorbate is providing enhanced preservative efficacy in compositions including benzalkonium chloride.

10

EXAMPLES 30 TO 33

A series of four (4) aqueous compositions were prepared by blending together the following components:

		Composition ⁽¹⁾			
		<u>30</u>	<u>31</u>	<u>32</u>	<u>33</u>
15	Prednisolone				
	Acetate, w/v%	-	0.1	0.1	0.1
	Sulfobutylether				
	β -cyclodextrin, w/v%	-	8.0	8.0	8.0
20	Stabilized chlorine				
	dioxide ⁽²⁾ , w/v%	.0075	-	-	-
	Potassium				
	sorbate, w/v%	-	0.5	0.5	0.5
	PH	7.4	6.5	5.5	4.5

(1) Each of the compositions includes USP water in a
 25 quantity sufficient to equal 100% w/v.

⁽²⁾ Product sold by Bio-Cide International Inc., under the trademark PUROGENE®

Each of these compositions was tested for preservative efficacy in accordance with (1) United States Preservative Efficacy Test (USPET) test criteria; (2) European Preservative Efficacy-A (EP-A) test criteria; and (3) European Preservative-B (EP-B) test criteria.

The test results for each of these compositions is set forth in the following table.

Composition	USPET	EP-A	EP-B
30	Pass	Fail	Fail
31	Pass	Fail	Fail
32	Pass	Fail	Pass
33	Pass	Pass	Pass

These results indicate that cyclodextrin compositions including either stabilized chlorine dioxide or potassium sorbate pass the USPET criteria. In particular, Compositions 31, 32 and 33 include both potassium sorbate and the cyclodextrin and pass the USPET criteria. At somewhat reduced pHs, as shown in Compositions 32 and 33, compositions including potassium sorbate and cyclodextrin pass the EP-B criteria (Composition 32) and even the EP-B and EP-A criteria (Composition 33).

Without wishing to limit the invention to any particular theory of operation, it is believed that the cyclodextrin component does not complex the sorbate component sufficiently to inhibit the sorbate from acting as an effective preservative. Also, the sorbate at more acidic conditions is a more effective preservative component.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the

5 following claims.

WHAT IS CLAIMED IS:

1. A composition comprising:
a liquid medium;
a cyclodextrin component in an amount in a range
of about 0.1% to about 30% (w/v); and
5 a chlorite component in an effective preserving
amount.
2. The composition of claim 1 wherein the liquid
medium is an aqueous liquid medium.
3. The composition of claim 1 wherein the
cyclodextrin component is selected from the group
consisting of β -cyclodextrin, derivatives of β -
cyclodextrin and mixtures thereof.
4. The composition of claim 1 wherein the chlorite
component is present in an amount of about 500 ppm (w/v)
or less.
5. The composition of claim 1 wherein the chlorite
component is present in an amount in a range of about 10
ppm(w/v) to about 200 ppm(w/v).
6. The composition of claim 1 wherein the chlorite
component is stabilized chlorine dioxide.
7. The composition of claim 1 which further
comprises an active component in an amount effective in
providing a desired effect to a human or an animal after
the composition is administered to the human or animal.

8. The composition of claim 7 wherein the active component is a pharmaceutically active component effective in providing a desired therapeutic effect to the human or animal after the composition is administered to the human or animal.

9. A composition comprising:
a liquid medium;
a cyclodextrin component in an amount in a range of about 0.1% to about 30% (w/v); and
a preservative component in an effective preserving amount, the preservative component having a greater preservative efficacy in the composition relative to an identical amount of benzalkonium chloride.

10. The composition of claim 9 wherein the preservative component forms a complex with the cyclodextrin component to a lesser degree than benzalkonium chloride.

11. The composition of claim 9 wherein the liquid medium is an aqueous liquid medium, and the preservative component is present in an amount of less than about 0.8% (w/v).

12. The composition of claim 9 wherein the preservative component is present in an amount in a range of about 10 ppm(w/v) to about 200 ppm(w/v).

13. The composition of claim 10 wherein the cyclodextrin component is selected from the group consisting of β -cyclodextrin, derivatives of β -cyclodextrin and mixtures thereof.

14. The composition of claim 9 wherein the preservative component is selected from the group consisting of chlorite components, sorbic acid components and mixtures thereof.

15. The composition of claim 9 wherein the preservative component is stabilized chlorine dioxide.

16. The composition of claim 9 wherein the preservative component is selected from the group consisting of sorbic acid, sorbates and mixtures thereof.

17. The composition of claim 9 which further comprises an active component in an amount effective in providing a desired effect to a human or an animal after the composition is administered to the human or animal.

18. The composition of claim 17 wherein the active component is a pharmaceutically active component effective in providing a desired therapeutic effect to the human or animal after the composition is administered to the human or animal.

19. The composition of claim 9 which is substantially free of inclusion complexes of the cyclodextrin component and the preservative component.

20. A composition comprising:
a liquid medium;
an active component in an amount effective in providing a desired effect to a human or an animal after the composition is administered to the human or animal;
a cyclodextrin component in an amount effective to increase the apparent solubility of the active

component in the liquid medium or to enhance the stability of the active component in the composition or to reduce
10 unwanted side effects of the active component; and

a preservative component in an effective preserving amount, the preservative component having greater preservative efficacy in the composition relative to an identical amount of benzalkonium chloride.

21. The composition of claim 20 wherein the liquid medium is an aqueous liquid medium.

22. The composition of claim 20 wherein the active component is a pharmaceutically active component effective in providing a desired therapeutic effect to the human or animal after the composition is administered to the human
5 or animal.

23. The composition of claim 21 wherein the active component is a pharmaceutically active component effective in providing a desired therapeutic effect to the human or animal after the composition is administered to the human
5 or animal.

24. The composition of claim 20 wherein the cyclodextrin component is selected from the group consisting of β -cyclodextrin, derivatives of β -cyclodextrin and mixtures thereof.

25. The composition of claim 20 wherein the cyclodextrin component is present in an amount in a range of about 0.1% to about 30% (w/v).

26. The composition of claim 20 wherein the preservative component forms a complex with the

cyclodextrin component to a lesser degree than does benzalkonium chloride.

27. The composition of claim 20 wherein the preservative component is present in an amount of about 1% (w/v) or less.

28. The composition of claim 20 wherein the preservative component is present in an amount in a range of about 10 ppm(w/v) to about 200 ppm(w/v).

29. The composition of claim 20 wherein the preservative component is selected from the group consisting of chlorite components, sorbic acid components and mixtures thereof.

30. The composition of claim 29 wherein the preservative component is stabilized chlorine dioxide.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/20060

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 06381 A (ALCON LAB INC ; ESPINO RAMON L (US); CASTILLO ERNESTO J (US)) 19 February 1998 (1998-02-19) page 13, line 8 - line 25	9-13, 17-28
X	EP 0 119 737 A (TAKEDA CHEMICAL INDUSTRIES LTD) 26 September 1984 (1984-09-26) examples 3,6-8,10	9-13, 17-28
X	US 5 663 170 A (IKEJIRI YOSHIFUMI ET AL) 2 September 1997 (1997-09-02) example 17	9-13, 17-28
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

7 December 1999

Date of mailing of the international search report

16/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Trifillieff-Riolo, S

INTERNATIONAL SEARCH REPORT

Intern. Appl. No.
PCT/US 99/20060

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Derwent Publications Ltd., London, GB; AN 1978-80903a XP002124917 EDO HIROSHI ET AL: "food preservatives" & JP 53 113017 A (ASAHI ELECTROCHEMICAL CO LTD), 1977 abstract</p>	9-14, 16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/20060

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9806381 A	19-02-1998	AU 709580 B AU 3914097 A CA 2232435 A EP 0877600 A	02-09-1999 06-03-1998 19-02-1998 18-11-1998
EP 0119737 A	26-09-1984	JP 59152320 A	31-08-1984
US 5663170 A	02-09-1997	AT 121295 T AU 633754 B AU 8170891 A CA 2048942 A DE 69109021 D DE 69109021 T DK 472327 T EP 0472327 A ES 2071227 T FI 913811 A,B, JP 2769253 B JP 5213757 A NO 177845 B PT 98643 A,B RU 2068260 C	15-05-1995 04-02-1993 20-02-1992 14-02-1992 24-05-1995 21-09-1995 08-05-1995 26-02-1992 16-06-1995 14-02-1992 25-06-1998 24-08-1993 28-08-1995 31-07-1992 27-10-1996
JP 53113017 A	03-10-1978	NONE	

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ BLACK BORDERS

☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

☒ FADED TEXT OR DRAWING

☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING

☐ SKEWED/SLANTED IMAGES

☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS

☐ GRAY SCALE DOCUMENTS

☒ LINES OR MARKS ON ORIGINAL DOCUMENT

☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.